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REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

APPLICATION FOR A PATENT

AND ACKNOWLEDGEMENT OF RECEIPT
(Section 30 (1) - Regulation 22)

The granting of a patent is hereby requested by the undermentioned applicant on the basis of the present application in duplicate.

OFFICIAL APPLICATION No.			S & F REFERENCE
21	01	9410015	JP/D1294

FULL NAME(S) OF APPLICANT(S)

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TITLE OF INVENTION

54	A PHARMACEUTICAL COMPOSITION

THE APPLICANT CLAIMS PRIORITY AS SET OUT ON THE ACCOMPANYING FORM P.2. THE EARLIEST PRIORITY CLAIMED IS:

COUNTRY: ZA NUMBER: 93/6619 DATE: 15.09.93

THIS APPLICATION IS FOR A PATENT OF ADDITION TO PATENT APPLICATION NO.

21	01	

THIS APPLICATION IS A FRESH APPLICATION IN TERMS OF SECTION 37 AND IS BASED ON APPLICATION NO.

21	01	

THIS APPLICATION IS ACCOMPANIED BY:

- [x] 1. Two copies of a complete specification of 8 pages.
- [ ] 2. Drawings of ... sheets.
- [x] 3. Publication particulars and abstract (Form P.8 in duplicate).
- [ ] 4. A copy of Figure ... of the drawings (if any) for the abstract.
- [ ] 5. An assignment of invention.
- [ ] 6. Certified priority document(s) .
- [ ] 7. Translation of the priority document(s).
- [ ] 8. An assignment of priority rights.
- [ ] 9. A copy of the Form P.2. and the specification of S.A. Patent Application No.
- [ ] 10. A declaration and power of attorney on Form P.3.
- [ ] 11. Request for ante-dating on Form P.4.
- [ ] 12. Request for classification on Form P.9.
- [ ] 13.

74 ADDRESS FOR SERVICE: SPOOR AND FISHER, SANDTON

Dated : 15TH DECEMBER 1994

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RECEIVED

H 03840

REGISTRAR OF PATENTS

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

COMPLETE SPECIFICATION

(Section 30(1) - Regulation 28)

OFFICIAL APPLICATION NO.			LODGING DATE	
21	01	9410015	22	15.12.94

INTERNATIONAL CLASSIFICATION	
51	A61K

FULL NAME(S) OF APPLICANT(S)	
71	WILLIAM HENRY DAVIS ; HENRY JOHN DAVIS

FULL NAME(S) OF INVENTOR(S)	
72	WILLIAM HENRY DAVIS; HENRY JOHN DAVIS

TITLE OF INVENTION	
54	A PHARMACEUTICAL COMPOSITION

H 03841

BACKGROUND OF THE INVENTION

Insomnia, particularly amongst older people, can be problematic. Not only is it disquieting for an insomniac not to be able to sleep but it becomes debilitating when the insomniac has not had sufficient sleep and is expected to perform stressful or strenuous tasks the next day.

SUMMARY OF THE INVENTION

According to one aspect of the invention a pharmaceutical composition comprises L-arginine and a metal salt together with a pharmaceutically acceptable carrier, adjuvant or dispersant.

The L-arginine is preferably in the form of L-arginine monohydrochloride (L-Arg HCl)

The pharmaceutical composition may also comprise Vitamin D_3.

The metal salt is preferably calcium carbonate, calcium glutamate or calcium sulphate. Most preferably it is calcium carbonate.

The ratio of L-arginine to metal salt is preferably from 5:1 to 7.5:1.

According to another aspect of the invention there is provided the use of a composition comprising L-arginine together with a metal salt in a method of treating insomnia in a human patient. The composition may also comprise vitamin D_3.

According to yet another aspect of the invention there is provided the use of a composition comprising L-arginine together with a calcium salt in a method of treatment and/or prophylaxis of osteoporosis in a human patient. The composition may also comprise Vitamin D_3.

According to yet another aspect of the invention there is provided the use of a composition comprising L-arginine together with a metal salt and Vitamin D_3 for use in neutralising low gastric pH levels in a human patient.

DESCRIPTION OF PREFERRED EMBODIMENTS

The invention provides a pharmaceutical composition which is useful inter alia in the treatment of insomnia. Insomnia is prevalent amongst adults but in normal, untraumatised children, it is rare if not non-existent. The present inventors have linked this low incidence of insomnia in children to the activity of growth hormone (somatostatin). Somatostatin, a protein containing a single polypeptide chain, has an effect on growth and anabolism generally. In particular, it controls the gain in body weight and also the rate of skeletal growth, inter alia by promoting the uptake of calcium into the bone structure.

The inventors have found that by combining L-arginine, a quasi-essential amino acid for human infants, which activates somatostatin, with a calcium salt and administering it to humans, sleep can be induced. The pharmaceutical compositions formulated by the inventors contain L-arginine monohydrochloride, a colourless, water-soluble crystal, and calcium carbonate ($CaCO_3$) in a ratio of from 5:1 to 7.5:1. Other metal salts, most notably calcium glutamate and calcium sulphate when combined with L-arginine, have also been found to have a similar effect.

The administration of this pharmaceutical composition has also been found to have the unexpected advantage of encouraging an uptake of calcium into the bone structure. This, especially in the case of menopausal woman, helps to counter or prevent osteoporosis.

Although the L-arginine monohydrochloride promotes the uptake of calcium and its deposition into the bone structure, it is still often found that a certain percentage of the calcium is not used by the body. This is automatically and quickly excreted from the body via the kidneys. This excess calcium thus causes

diuresis which tends to limit the effectiveness of the composition of the invention in preventing insomnia because the diuresis itself tends to wake the patient. It has been found, however, that the addition of Vitamin D_3 to the composition reduces calcium excretion as the active form of Vitamin D_3, namely 1,25 dihydroxy Vitamin D_3, binds the calcium and enhances its deposition in the bone structure. Thus, the addition of Vitamin D_3 further promotes the uptake of calcium and its deposition into bone and the sleep induction effect of the compositions of the invention is also further enhanced.

The L-arginine monohydrochloride in the pharmaceutical compositions of the invention forms nitric oxide in the body. It is known that nitric oxide promotes the formation of 25 dihydroxy-Vitamin D_3, the active form of Vitamin D_3. The L-arginine monohydrochloride and Vitamin D_3 thus complement each other and their administration together thus further enhances the efficacy of the composition.

The nitric oxide that is formed by the L-arginine monohydrochloride in the body, apart from promoting the above reaction, also works on receptors in the oesophagus, thereby normalising peristalsis of the oesophagus and preventing reflux in the oesophagus. It also relaxes the smooth musculature of the gastrointestinal tract, so preventing pyloric valve spasm which, in turn, prevents gastric stasis. The combination of the calcium carbonate and the L-arginine, a basic amino acid, acts as an antacid which tends to neutralise low pH levels in the stomach of a patient. These are added benefits of the pharmaceutical compositions of the invention.

The physical nature of the L-arginine monohydrochloride and the metal salts and the Vitamin D_3 (dry powder form of 100 000 IU per gram) in the compositions of the present invention make it possible for them to be administered orally, for example, in the form of a capsule. A typical unit dosage of the composition of

the invention would comprise a 500 mg capsule, containing about 414 mg of L-arginine monohydrochloride, about 84 mg of calcium carbonate and about 2 mg of Vitamine D_3, and the rest being a suitable pharmaceutical carrier, diluent or adjuvant. Such a 500 mg capsule may alternatively contain 439.5 mg of L-arginine monohydrochloride, about 58.5 mg of calcium carbonate and about 2 mg of Vitamin D_3, and the rest being a suitable pharmaceutical carrier, diluent or adjuvant. Such a 500 mg capsule may alternatively contain 439.5 mg of L-arginine monohydrochloride, about 58.5 mg of calcium carbonate and about 2 mg of Vitamin D_3 powder. Typically, two of such capsules per day will be required by an insomniac, giving an effective dosage of 879 mg of L-arginine monohydrochloride and 117 mg of calcium carbonate and 4 mg of Vitamin D_3 per day.

For maximum benefit in alleviating insomnia, the composition should be administered at night, some time before the insomniac goes to bed, to induce sleep and to maintain this effect for at least part of the night.

CLAIMS

1. A pharmaceutical composition comprising L-arginine and a metal salt together with a pharmaceutically acceptable carrier, adjuvant or dispersant.

2 A pharmaceutical composition according to claim 1 wherein the L-arginine is in the form of L-arginine monohydrochloride.

3 A pharmaceutical composition according to claim 2 or claim 3 which also comprises Vitamin D_3.

4 A pharmaceutical composition according to any one of claims 1 to 3 wherein the metal salt is calcium carbonate, calcium glutamate or calcium sulphate.

5 A pharmaceutical composition according to claim 4 wherein the metal salt is calcium carbonate.

6 A pharmaceutical composition according to any one of the preceeding claims whrein the ratio of L-arginine to metal salt is from 5:1 to 7.5:1.

7 A composition according to any one of claims 1 to 6 for use in a method of treating insomnia in a human patient.

8 A composition according to any one of claims 4 to 6 for use in a method of treatment and/or prophylaxis osteoporosis in a human patient.

9 A composition according to any one of claims 1 to 6 for use in a method of neutralising low gastric pH levels in a patient.

10 A composition according to any one of claims 1 to 6 for use in a method of relaxing the smooth musculature of the gastrointestinal tract thereby preventing gastric stasis.

11 A composition according to any one of claims 1 to 6 for use in a method of normalising peristalsis of the oesophagus thereby preventing reflux in the oesophagus.

12 A pharmaceutical composition according to claim 1 substantially as herein described with reference to the illustrative examples

DATED THIS 15TH DAY OF DECEMBER 1994

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APPLICANTS PATENT ATTORNEYS

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DIALOG(R)File 399:CA SEARCH(R)

126190939 CA: 126(14)190939d PATENT
A pharmaceutical compositions containing arginine and a calcium salt for the treatment of insomnia
INVENTOR(AUTHOR): Davis, William Henry; Davis, Henry John
LOCATION: S. Afr.
ASSIGNEE: Davis, William Henry; Davis, Henry John
PATENT: South Africa ; ZA 9410015 A DATE: 19951108
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126:190939 A pharmaceutical compositions containing arginine and a calcium salt for the treatment of insomnia. Davis, William Henry; Davis, Henry John (Davis, William Henry, S. Afr.; Davis, Henry John). S. African ZA 9410015 A 19951108, 9 pp. (English). CODEN: SFXXAB. APPLICATION: ZA 1994-10015 19941215. PRIORITY: ZA 1993-6619 19930915.

AB A pharmaceutical compn. comprising L-arginine and a calcium salt together with a pharmaceutically acceptable carrier, adjuvant or dispersant is claimed (no data).